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## SEARCH REQUEST FORM

Access DB#

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MAY -4 2000

Scientific and Technical Information Center

(STIC)  
Requester's Full Name: RICHARD SCHWARTZ Examiner #: 76557 Date: 5/4/04  
Art Unit: 1635 Phone Number 301 20762 Serial Number: 09/786055  
Mail Box and Bldg/Room Location: Box 2C18 Results Format Preferred (circle): PAPER DISK E-MAIL  
Box 2C01-050

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: PHOSPHOROXIDESInventors (please provide full names): Christian Belmant, Jean-Jacque Fournie,  
Marc Bonneville, Marie-Alix PeyratEarliest Priority Filing Date: 9/1/98

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the following structures

Where:

 $n = 2-22$  $Ca^{++} = \text{cation}$  $R_1 = CH_3 \text{ or } CH_2CH_3$  $R_2 = \text{anything}$ 

C. Chan

Rush

## STAFF USE ONLY

Searcher: D. SchweiberSearcher Phone #: 272-2526Searcher Location: Remsen Eol A61Date Searcher Picked Up: 5/6Date Completed: 5/6Searcher Prep & Review Time: 13Clerical Prep Time: 61Online Time: 61

## Type of Search

NA Sequence (#) \_\_\_\_\_

AA Sequence (#) \_\_\_\_\_

Structure (#) 1

Bibliographic \_\_\_\_\_

Litigation \_\_\_\_\_

Fulltext \_\_\_\_\_

Patent Family \_\_\_\_\_

Other \_\_\_\_\_

## Vendors and cost where applicable

STN

268.80

Dialog \_\_\_\_\_

Questel/Orbit \_\_\_\_\_

Dr.Link \_\_\_\_\_

Lexis/Nexis \_\_\_\_\_

Sequence Systems \_\_\_\_\_

WWW/Internet \_\_\_\_\_

Other (specify) \_\_\_\_\_



# **STIC Search Report**

## **Biotech-Chem Library**

**STIC Database Tracking Number: 121086**

**TO: Richard Schnizer**  
**Location: rem/2c01/2c18**  
**Art Unit: 1635**  
**Thursday, May 06, 2004**

**Case Serial Number: 09/786055**

**From: David Schreiber**  
**Location: Biotech-Chem Library**  
**Remsen E01A61**  
**Phone: 272-2526**

**david.schreiber@uspto.gov**

### **Search Notes**

=&gt; fil hcaplus

FILE 'HCAPLUS' ENTERED AT 10:20:12 ON 06 MAY 2004

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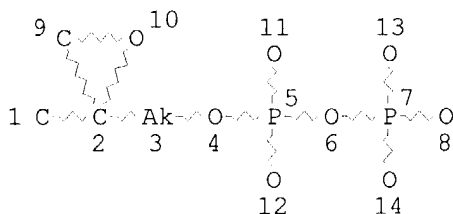
FILE COVERS 1907 - 6 May 2004 VOL 140 ISS 19

FILE LAST UPDATED: 5 May 2004 (20040505/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=&gt; d que l13

L1 17 SEA FILE=HCAPLUS BELMANT C?/AU  
 L2 96 SEA FILE=HCAPLUS FOURNIE J?/AU  
 L3 129 SEA FILE=HCAPLUS BONNEVILLE M?/AU  
 L4 80 SEA FILE=HCAPLUS PEYRAT M?/AU  
 L5 231 SEA FILE=HCAPLUS (L1 OR L2 OR L3 OR L4)  
 L8 STR



## NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS M2-X22 C AT 3

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 14

## STEREO ATTRIBUTES: NONE

L11 10 SEA FILE=REGISTRY SSS FUL L8

L12 11 SEA FILE=HCAPLUS L11

L13 4 SEA FILE=HCAPLUS L12 AND L5

=&gt; d ibib abs hitstr l13 1-4

L13 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:463707 HCAPLUS  
 DOCUMENT NUMBER: 135:207791  
 TITLE: Characterization of Phosphoantigens by  
 High-Performance Anion-Exchange Chromatography-  
 Electrospray Ionization Ion Trap Mass Spectrometry and  
 Nanoelectrospray Ionization Ion Trap Mass Spectrometry  
 AUTHOR(S): Pont, Frederic; Luciani, Beatrice; **Belmant,**  
**Christian; Fournie, Jean Jacques**  
 CORPORATE SOURCE: Service de Spectrometrie de Masse de l'IFR 30, CHU  
 Purpan, Toulouse, 31024, Fr.  
 SOURCE: Analytical Chemistry (2001), 73(15), 3562-3569  
 CODEN: ANCHAM; ISSN: 0003-2700  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

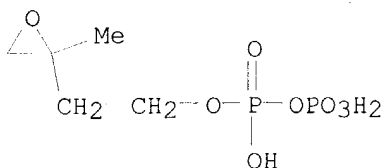
AB New phosphorylated microbial metabolites referred to as phosphoantigens activate immune responses in humans. Although these mols. have leading applications in medical research, no direct method allows their rapid and unambiguous structural identification. Here, we interfaced online high performance anion-exchange chromatog. (HPAEC) with electrospray ionization ion trap mass spectrometry (ESI-ITMS) to identify such pyrophosphorylated mols. A self-regenerating anion suppressor located upstream of electrospray ionization enabled the simultaneous detection of pyrophosphoester by conductimetry, UV and MS. By HPAEC-ITMS and HPAEC-ITMS2, a single run permitted characterization of reference phosphoantigens and of related structures. Although all compds. were resolved by HPAEC, MS enabled their detection and identification by [M - H]- and fragment ions. Isobaric phosphoantigen analogs were also separated by HPAEC and distinguished by MS2. The relevance of this device was demonstrated for phosphoantigens anal. in human urine and plasma. Furthermore, identification of natural phosphoantigens by automatically generated 2D mass spectra from nano-ESI-ITMS is presented. This last technique permits the simultaneous performance of mol. screening of natural phosphoantigen exts. and their identification.

IT 115914-67-5

RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)  
 (characterization of phosphoantigens by anion-exchange  
 HPLC-electrospray ionization ion trap mass spectrometry and  
 nanoelectrospray ionization ion trap mass spectrometry)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:119873 HCAPLUS

DOCUMENT NUMBER: 137:92275

TITLE: A chemical basis for selective recognition of

nonpeptide antigens by human  $\delta$  T cells. [Erratum to document cited in CA133:320819]

AUTHOR(S): **Belmant, Christian**; Espinosa, Eric; Halary, Franck; Tang, Yong; **Peyrat, Marie-Alix**; Sicard, Helene; Kozikowski, Aalan; Buelow, Roland; Poupot, Remy; **Bonneville, Marc**; **Fournie, Jean-Jacques**

CORPORATE SOURCE: INSERM U395, CHU Purpan, Toulouse, 31024, Fr.

SOURCE: FASEB Journal (2000), 14(13), 2128  
 CODEN: FAJOEC; ISSN: 0892-6638  
 URL: <http://www.fasebj.org/cgi/doi/10.1096/fj.99-0909fje>

PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal

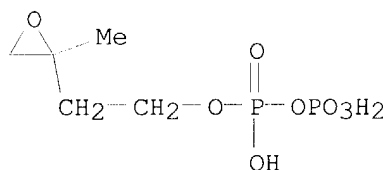
LANGUAGE: English

AB The correct URL link (web address) is <http://www.fasebj.org/cgi/doi/10.1096/fj.99-0909fje>.

IT **115914-67-5**  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (structure-function anal. of T-cell recognition of (Erratum))

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



L13 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:655984 HCAPLUS

DOCUMENT NUMBER: 133:320819

TITLE: A chemical basis for selective recognition of nonpeptide antigens by human  $\delta$  T cells

AUTHOR(S): **Belmant, Christian**; Espinosa, Eric; Halary, Franck; Tang, Yong; **Peyrat, Marie-Alix**; Sicard, Helene; Kozikowski, Alan; Buelow, Roland; Poupot, Remy; **Bonneville, Marc**; **Fournie, Jean-Jacques**

CORPORATE SOURCE: INSERM U395, CHU Purpan, Toulouse, 31024, Fr.

SOURCE: FASEB Journal (2000), 14(12), 1669-1670  
 CODEN: FAJOEC; ISSN: 0892-6638

PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

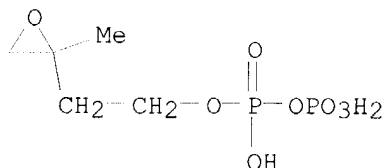
AB Human  $\gamma\delta$  T lymphocytes activate their immune function upon TCR-mediated recognition of antigens not associated with MHC mols. Because different non-peptide phosphorylated antigens (phosphoantigens) are selectively recognized by  $\gamma\delta$  T cells, the authors clarified its mol. basis through the structure-function relation of novel synthetic phosphoantigens.

IT 115914-67-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study) (structure-function anal. of T-cell recognition of)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



L13 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:161295 HCAPLUS

DOCUMENT NUMBER: 132:194500

TITLE: Preparation of phosphoepoxides and their application in activating Ty982 lymphocytes of primates

INVENTOR(S): **Belmant, Christian; Fournie, Jean-jacques; Bonneville, Marc; Peyrat, Marie-alix**

PATENT ASSIGNEE(S): Institut National De La Sante Et De La Recherche Medicale, Fr.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012519	A1	20000309	WO 1999-FR2057	19990827
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2782722	A1	20000303	FR 1998-10914	19980901
FR 2782722	B1	20010112		
CA 2341578	AA	20000309	CA 1999-2341578	19990827
AU 9954265	A1	20000321	AU 1999-54265	19990827
EP 1109818	A1	20010627	EP 1999-940246	19990827
EP 1109818	B1	20021106		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002523515	T2	20020730	JP 2000-567540	19990827
AT 227296	E	20021115	AT 1999-940246	19990827
PT 1109818	T	20030228	PT 1999-940246	19990827

ES 2187184 T3 20030516 ES 1999-940246 19990827  
 PRIORITY APPLN. INFO.: FR 1998-10914 A 19980901  
 WO 1999-FR2057 W 19990827

OTHER SOURCE(S): CASREACT 132:194500

AB The invention concerns compds. comprising at least a phosphoepoxide group of formula  $R_1C(CH_2O)(CH_2)_nOP(O)(O-Cat+)OP(O)(O-Cat+)O^-$  ( $R_1 = Me, Et$ ;  $Cat+ =$  organic or mineral cation;  $n = 2-20$ ). The invention also concerns their preparation methods and applications, particularly in therapy and for activating Ty982 lymphocytes of primates. For example, the Na salt of 3,4-epoxy-3-methylbutyl diphosphate was prepared in 4 steps: (1) preparation of 3-methyl-3-butenyl tosylate from tosyl chloride and isopentenol; (2) preparation of the ammonium salt of 3-methyl-3-butenyl diphosphate from tris(tetrabutylammonium) hydrogen pyrophosphate and 3-methyl-3-butenyl tosylate; (3) the bromination of the 3-methyl-3-butenyl diphosphate by bromine water; and (4) cyclization in aqueous ammonia.

IT **259793-68-5P**, 3,4-Epoxy-3-methylbutyl tetrasodium triphosphate

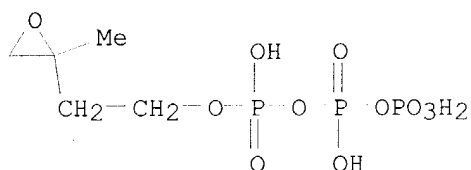
**259793-69-6P**,  $\alpha, \gamma$ -Bis(3,4-epoxy-3-methylbutyl) trisodium triphosphate **259793-70-9P**,  $\gamma$ -(3,4-Epoxy-3-methylbutyl) trisodium uridine-5'-triphosphate

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation and activation of Ty982 lymphocytes by)

RN 259793-68-5 HCAPLUS

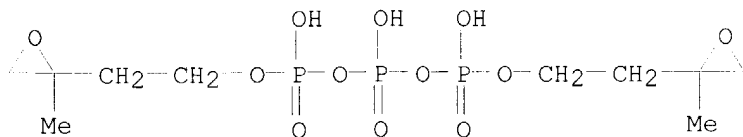
CN Triphosphoric acid, P-[2-(2-methyloxiranyl)ethyl] ester, tetrasodium salt (9CI) (CA INDEX NAME)



●4 Na

RN 259793-69-6 HCAPLUS

CN Triphosphoric acid, P,P''-bis[2-(2-methyloxiranyl)ethyl] ester, trisodium salt (9CI) (CA INDEX NAME)



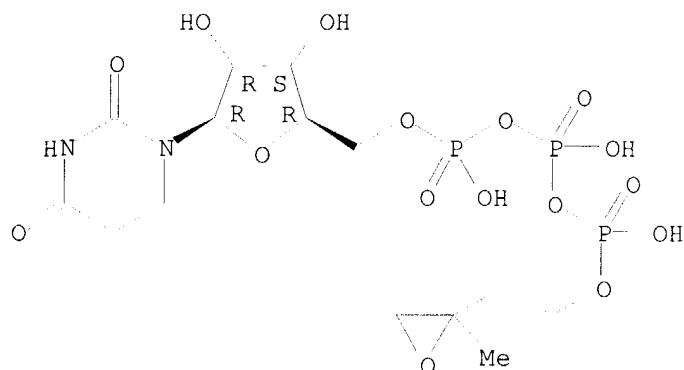
●3 Na

RN 259793-70-9 HCAPLUS

CN Uridine 5'-(tetrahydrogen triphosphate), P''-[2-(2-methyloxiranyl)ethyl]

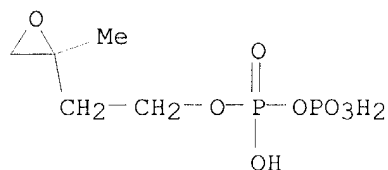
ester, trisodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●3 Na

IT **259793-67-4P**, 3,4-Epoxy-3-methylbutyl trisodium diphosphate  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation, toxicity and activation of T<sub>γ</sub>982 lymphocytes by)  
 RN 259793-67-4 HCAPLUS  
 CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester, trisodium salt (9CI) (CA INDEX NAME)



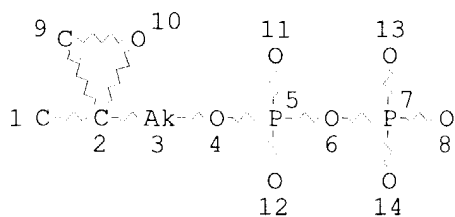
●3 Na

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d que 114

L1 17 SEA FILE=HCAPLUS BELMANT C?/AU  
 L2 96 SEA FILE=HCAPLUS FOURNIE J?/AU  
 L3 129 SEA FILE=HCAPLUS BONNEVILLE M?/AU  
 L4 80 SEA FILE=HCAPLUS PEYRAT M?/AU  
 L5 231 SEA FILE=HCAPLUS (L1 OR L2 OR L3 OR L4)  
 L8 STR





## NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS M2-X22 C AT 3

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 14

## STEREO ATTRIBUTES: NONE

L11 10 SEA FILE=REGISTRY SSS FUL L8

L12 11 SEA FILE=HCAPLUS L11

L13 4 SEA FILE=HCAPLUS L12 AND L5

L14 7 SEA FILE=HCAPLUS L12 NOT L13

=&gt; d ibib abs hitstr l14 1-7

L14 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:55097 HCAPLUS

DOCUMENT NUMBER: 140:231385

TITLE: Crystal structure of the C67A mutant of isopentenyl diphosphate isomerase complexed with a mechanism-based irreversible inhibitor

AUTHOR(S): Wouters, J.; Oudjama, Y.; Stalon, V.; Droogmans, L.; Poulter, C. D.

CORPORATE SOURCE: Institut de Recherches Microbiologiques J.M. Wiame, Brussels, Belg.

SOURCE: Proteins: Structure, Function, and Bioinformatics (2003), Volume Date 2004, 54(2), 216-221

CODEN: PSFBAF

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Isopentenyl diphosphate isomerase (I) is a key enzyme in the biosynthesis of isoprenoids. The mechanism of the isomerization reaction involves protonation of the unactivated C:C bond in the substrate. Anal. of the 1.97 Å crystal structure of the inactive C67A mutant of Escherichia coli I complexed with the mechanism-based inactivator, 3,4-epoxy-3-methyl-1-Bu diphosphate, was in agreement with an isomerization mechanism involving Glu-116, Tyr-104, and Cys-67. In particular, the results were consistent with a mechanism for I where Glu-116 is involved in the protonation step and Cys-67 in the elimination step.

IT **115914-67-5D**, complexes with isopentenyl diphosphate isomerase C67A mutant

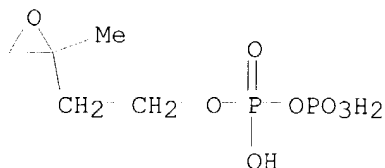
RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); BIOL

(Biological study); PROC (Process)

(crystal structure of Escherichia coli isopentenyl diphosphate isomerase C67A mutant complexed with a mechanism-based irreversible inhibitor)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:678965 HCAPLUS

DOCUMENT NUMBER: 139:196245

TITLE: Methods for producing  $\gamma\delta$  T-cells

INVENTOR(S): Romagne, Francois; Laplace, Catherine

PATENT ASSIGNEE(S): Innate Pharma, Fr.

SOURCE: PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070921	A1	20030828	WO 2003-FR585	20030221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
FR 2836483	A1	20030829	FR 2002-2305	20020222

PRIORITY APPLN. INFO.: FR 2002-2305 A 20020222

AB The invention discloses methods for producing lymphocytic cells, as well as tools, reagents, and kits useful for implementing same. More particularly, the invention discloses methods for preparing  $\gamma\delta$  T cells, adapted to industrial production of functional cells of pharmaceutical quality in large amts. The invention also concerns methods for activating  $\gamma\delta$  T cells, devices adapted to the methods, as well as the resulting cell comps. and their human or animal  $\gamma\delta$  T cells, and can be used in pharmaceuticals, therapeutics, expts., cosmetics, industrial research among others.

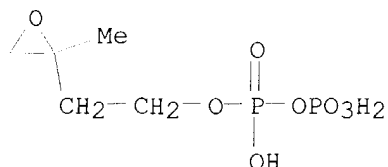
IT 115914-67-5 586354-83-8 586354-84-9

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(methods for producing  $\gamma\delta$  T-cells)

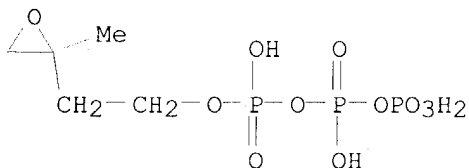
RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



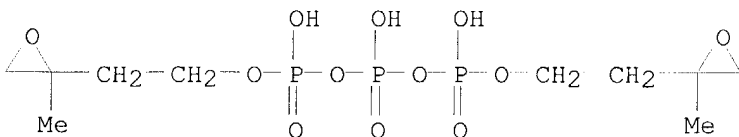
RN 586354-83-8 HCAPLUS

CN Triphosphoric acid, P-[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



RN 586354-84-9 HCAPLUS

CN Triphosphoric acid, P,P''-bis[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



REFERENCE COUNT:

4

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:247400 HCAPLUS

DOCUMENT NUMBER: 139:145735

TITLE: Catalytic mechanism of Escherichia coli isopentenyl diphosphate isomerase involves Cys-67, Glu-116, and Tyr-104 as suggested by crystal structures of complexes with transition state analogues and irreversible inhibitors

AUTHOR(S): Wouters, J.; Oudjama, Y.; Barkley, Sam J.; Tricot, C.; Stalon, V.; Droogmans, L.; Poulter, C. Dale

CORPORATE SOURCE: Institut de Recherches Microbiologiques J.M. Wiame, Brussels, 1070, Belg.

SOURCE: Journal of Biological Chemistry (2003), 278(14), 11903-11908

CODEN: JBCHA3; ISSN: 0021-9258

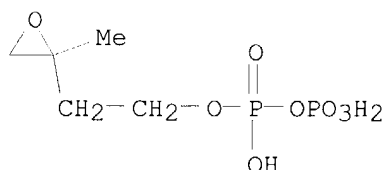
PUBLISHER: American Society for Biochemistry and Molecular Biology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Isopentenyl diphosphate (IPP)-dimethylallyl diphosphate isomerase (I) is a key enzyme in the biosynthesis of isoprenoids. The reaction involves protonation and deprotonation of the isoprenoid unit and proceeds through a carbocationic transition state. Here, anal. of crystal structures (2 Å) of complexes of E. coli I with a transition state analog, N,N-dimethyl-2-amino-1-Et diphosphate (NIPP), and with a covalently attached irreversible inhibitor, 3,4-epoxy-3-methyl-1-Bu diphosphate (EIPP), indicated that Glu-116, Tyr-104, and Cys-67 are involved in the antarafacial addition/elimination of protons during isomerization. In NIPP, the pos. charged ammonium group mimics the putative carbocation formed by protonation of the double bond in IPP; the inhibitor forms a stable noncovalent complex with I. EIPP is an irreversible inhibitor that forms a covalent bond to Cys-139 in yeast I. Anal. of the crystal structures of complexes between those transition state analogs and E. coli I provides evidence for the involvement of Cys-67 and Glu-116 and suggests that Tyr-104 may also be part of the catalytic machinery. This work provides a new perspective on the reaction mechanism.

IT **115914-67-5D**, complexes with isopentenyl diphosphate isomerase  
 RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); BIOL (Biological study); PROC (Process)  
 (crystal structure of Escherichia coli isopentenyl diphosphate isomerase complexed with ligands)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2002:710130 HCAPLUS  
 DOCUMENT NUMBER: 137:261824  
 TITLE: Quantitative Structure-Activity Relations for  $\gamma\delta$  T Cell Activation by Phosphoantigens  
 AUTHOR(S): Gossman, William; Oldfield, Eric  
 CORPORATE SOURCE: Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA  
 SOURCE: Journal of Medicinal Chemistry (2002), 45(22), 4868-4874  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB  $\gamma\delta$  T cells help contribute to innate immunity and are activated by the natural phosphoantigens produced by the organisms

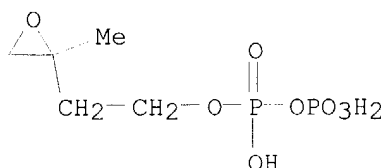
responsible for causing, for example, tuberculosis, malaria, tularemia, and plague. They are also activated by synthetic phosphoantigens and are cytotoxic to tumor cells. Here, we show that it is now possible to accurately predict  $\gamma\delta$  T cell activation by both natural and synthetic phosphoantigens by using the quant. structure-activity relationship (QSAR) techniques commonly used in drug design. This approach should be of use in developing novel immunotherapeutic agents as well as contributing to a better understanding of the immune system's response to infectious agents.

IT 115914-67-5

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(quant. structure-activity relations for  $\gamma\delta$  T cell activation by phosphoantigens)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1993:539564 HCAPLUS

DOCUMENT NUMBER: 119:139564

TITLE: Biosynthesis of Archaeobacterial lipids in Halobacterium halobium and Methanobacterium thermoautotrophicum

AUTHOR(S): Zhang, Donglu; Poulter, C. Dale

CORPORATE SOURCE: Dep. Chem., Univ. Utah, Salt Lake City, UT, 84112, USA

SOURCE: Journal of Organic Chemistry (1993), 58(15), 3919-22  
CODEN: JOCEAH; ISSN: 0022-3263

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB The core membrane lipids in archaeobacteria are isoprenoid ether derivs., e.g. I, of glycerol instead of fatty acid esters found in other organisms. Activities for three key enzymes in membrane lipid biosynthesis, isopentenyl diphosphate (IPP) isomerase, geranylgeranyl diphosphate (GGPP)

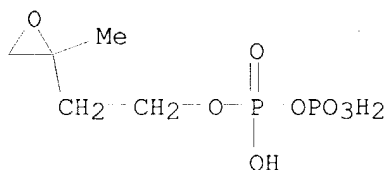
synthase, and 3-O-geranylgeranylglyceryl phosphate (GGGP) synthase were found in the cytosolic fractions of cell-free homogenates from the strict anaerobe *Methanobacterium thermoautotrophicum* and the extreme halophile *Halobacterium halobium*. The substrate selectivities of GGGP synthase from both sources were similar and indicate a common pathway for biosynthesis of the isoprenoid compds. in core membrane lipids from methanogenic and halophilic archaeobacteria.

IT **115914-67-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and inhibition by, of isopentenyl diphosphate isomerase)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



L14 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1992:587103 HCAPLUS

DOCUMENT NUMBER: 117:187103

TITLE: Isopentenyl-diphosphate isomerase: irreversible inhibition by 3-methyl-3,4-epoxybutyl diphosphate

AUTHOR(S): Lu, Xiang J.; Christensen, Dale J.; Poulter, C. Dale

CORPORATE SOURCE: Dep. Chem., Univ. Utah, Salt Lake City, UT, 84112, USA

SOURCE: Biochemistry (1992), 31(41), 9955-60

CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Isopentenyl diphosphate isomerase (EC 5.3.3.2) (I) catalyzes the 1,3-allylic rearrangement of the homoallylic substrate, isopentenyl diphosphate, to its allylic isomer, dimethylallyl diphosphate. The incubation of yeast I with 3-methyl-3,4-epoxybutyl diphosphate (II) resulted in a time-dependent 1st-order loss of activity characteristics of an active-site-directed irreversible process, where  $k_2 = 0.63 \text{ min}^{-1}$  and  $K_i = 0.37 \text{ } \mu\text{M}$ . A 1:1 covalent enzyme-inhibitor (E-I) complex was formed upon incubation with [1- $^{14}\text{C}$ ]II. Inhibited I was treated with trypsin to give 2 radioactive fragments, which were purified by reversed-phase HPLC on a C18 column. The modified amino acid in each fragment was identified as Cys-139 by sequencing the radiolabeled peptides. The incubation of I with [2,4,5- $^{13}\text{C}$ ]II gave a  $^{13}\text{C}$ -labeled E-I complex. A  $^1\text{H}$ - $^{13}\text{C}$  heteronuclear multiquantum correlation spectrum had strong cross-peaks at 1.2/28 and 2.9/48 ppm, which were assigned to the labeled Me group and C4 methylene group, resp., of II. In addition, a weak signal at 2.17/42 ppm may be from the C2 methylene group. A comparison of these chemical shifts with those of a synthetic adduct isolated from treatment of II with cysteine indicated that Cys-139 attacks the C4 atom of II to generate a thioether linkage between the enzyme and the inhibitor.

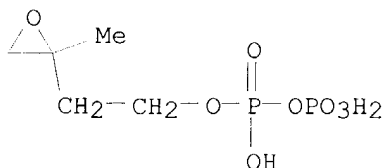
IT **115914-67-5**

RL: BIOL (Biological study)

(isopentenyl diphosphate isomerase inhibition by, mechanism of, active site cysteine-139 modification in relation to)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)

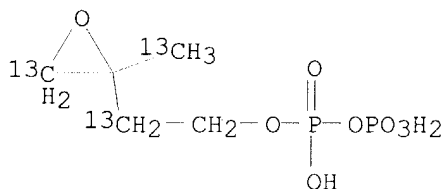


IT **143445-82-3P 143445-84-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and isopentenyl diphosphate isomerase inhibition by)

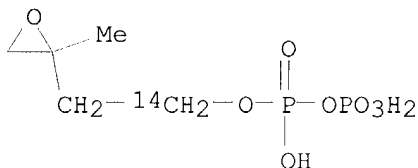
RN 143445-82-3 HCAPLUS

CN Diphosphoric acid, mono[2-[2-(methyl-13C)oxiranyl-3-13C]ethyl-2-13C] ester (9CI) (CA INDEX NAME)



RN 143445-84-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl-1-14C] ester (9CI) (CA INDEX NAME)



L14 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:524850 HCAPLUS

DOCUMENT NUMBER: 109:124850

TITLE: Isopentenyl-diphosphate isomerase: inactivation of the enzyme with active-site-directed irreversible inhibitors and transition state analogs

AUTHOR(S): Muehlbacher, Manfred; Poulter, C. Dale

CORPORATE SOURCE: Dep. Chem., Univ. Utah, Salt Lake City, UT, 84112, USA

SOURCE: Biochemistry (1988), 27(19), 7315-28

CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Seven analogs of isopentenyl diphosphate and dimethylallyl diphosphate containing F, epoxy, and ammonium functional groups irreversibly inhibited isopentenyl diphosphate isomerase (EC 5.3.3.2) from *Claviceps purpurea*. Inactivation kinetics, substrate protection studies, and labeling expts.

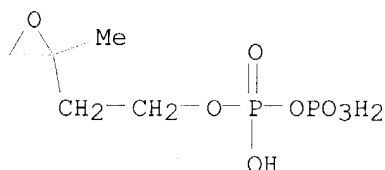
demonstrated that the analogs interacted stoichiometrically with the active site of the enzyme. Radioactive enzyme-inactivator complexes were stable to extended dialysis and treatment with chaotropic reagents. The complexes resulting from inactivation of isomerase by 3-(fluoromethyl)-3-buten-1-yl diphosphate (I) and 3,4-epoxy-3-methyl-1-Bu diphosphate were also stable to ion-exchange chromatog. and gel electrophoresis. Stoichiometric release of F<sup>-</sup> occurred during inactivation of isomerase with I. This observation was consistent with SN2 or SN2' displacement of F by an active-site nucleophile with concomitant covalent attachment of the inactivator to the enzyme. 2-(Dimethylamino)ethyl diphosphate (II) formed a stable noncovalent complex with isomerase with a dissociation constant of  $< 1.2 \times 10^{-10}$  M. The enzyme-inhibitor complex was stable in 6M urea, but the inhibitor was partially released upon treatment with SDS and 2-mercaptoethanol at 37° for 1 h. The results indicated that II is a transition-state/reactive intermediate analog where the pos. charged ammonium group mimics a tertiary carbocationic species in the enzyme-catalyzed reaction.

IT **115914-82-4P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and isopentenyl diphosphate isomerase of *Claviceps purpurea* inactivation by)

RN 115914-82-4 HCAPLUS

CN Diphosphoric acid, labeled with phosphorus-32, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)



IT **115914-67-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and kinetics of isopentenyl diphosphate isomerase of *Claviceps purpurea* inactivation by)

RN 115914-67-5 HCAPLUS

CN Diphosphoric acid, mono[2-(2-methyloxiranyl)ethyl] ester (9CI) (CA INDEX NAME)

